REMARKS

Claims 6-34 were pending in the application. Claim 30 has been amended and claim 35 has been added. Accordingly, claims 7-17, 22-29, and 32-33, and 35 will remain pending, and claims 6, 18-21, 30-31, and 34 will stand withdrawn.

Amendment and cancellation of the claims herein are not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action or any previous Office Action, and were done solely to expedite prosecution of the instant application. Applicants hereby reserve the right to prosecute the claims as originally filed, or similar claims, in one or more continuation or divisional applications.

In view of the present amendments and remarks, Applicants believe that the claims are in condition for allowance. Should the Examiner disagree, Applicants respectfully request the Examiner to contact Applicants' undersigned representative by telephone so that an interview may be scheduled prior to the mailing of any final Office Action.

Withdrawal of Claims

The Examiner has indicated that claim 30 has been withdrawn from consideration as being drawn to a non-elected species. Applicants disagree. Moreover, claim 30 has been amended to depend from claim 29 directed to an expression vector and which is not withdrawn.

Rejection of Claims 7-17, 22-29, 32 and 33 Under 35 USC 112, First Paragraph

The Examiner has rejected claims 7-17, 22-29, 32 and 33 under 35 USC 112, first paragraph as lacking written description. Specifically, the Examiner alleges that there is no support in the specification for "a polypeptide spacer" other than the CD8 hinge. Applicants respectfully disagree. Applicants respectfully point out that there is support for spacers on, for example, page 6 lines 10-14 of the specification.

Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection of Claims 7-17, 23-25, 28, 29, 32 and 33 Under 35 USC 103(a)

The Examiner has rejected claims 7-17, 23-25, 28, 29, 32 and 33 Under 35 USC 103(a) as being unpatentable over Chung et al. in view of Sette et al. Applicant respectfully traverse this rejection.

The Examiner has focused on a narrow interpretation of the claims. Specifically, the Examiner does not discuss other non-single chain TCR fusions or those to the transmembrane/cytoplasmic domains of CD8 or CD16 receptors provided in claim 32. If the Examiner insists on maintaining this rejection, Applicants respectfully request that the Examiner address the full scope of the claims.

Chung et al. teach a nucleic acid encoding a human single chain TCR wherein the human TCR Vα and Vβ chains are linked by a peptide and the human single-chain TCR is further linked to the CD3 ζ region by a polypeptide spacer. Chung et al. did not teach such a construct encoding a non-human TCR. In addition, the TCR disclosed by Chung et al. is specific to a peptide derived from myelin basic protein not a tumor associated antigen. Given that human and non-human TCR have distinct amino acid sequences and are functionally distinct, nothing disclosed in Chung et al. would lead one skilled in the art to assume that a similar construct encoding a non-human TCR would retain the functional activity (i.e. human HLA restriction and specificity to tumor associated antigen) provided in claim 32 of the current application.

Sette et al. shows that HLA-A*0201/K^b transgenic mice when immunized with viral peptides are capable of producing T cells (i.e. CTLs) with nonhuman TCRs restricted to the chimeric HLA-A*0201/K^b molecule. However, Sette et al. does not exemplify generation of T cells in these mice that are restricted against the native (i.e. non-chimeric) HLA molecule. In contrast, Applicant showed generation of T-cell from HLA-A2.1 transgenic mice are capable of recognizing HER-2/neu antigen in the context of native HLA-A2.1 or on HLA-A2.1-positive tumor cells (see Examples 1 and 2 of current application). Sette et al. also does not disclose generation of a T cells with nonhuman TCR specific for a tumor-associated antigens. In fact, Sette et al. teaches that the properties of the peptides inducing an HLA-A*0201/K^b –restricted T cell response in the HLA-A*0201/K^b transgenic mice may differ from those identified as immunodominant and HLA-A*0201-bound antigens in humans (Page 5590, Table IV). Thus it would be difficult to extrapolate from the results shown in Sette et al. for viral peptides to other antigens including those identified from human tumors.

Sette et al. also does not disclose use of T cells to generate of a nucleic acid molecule of claim 32 of the current application. CTL activity described by Sette et al. represents that observed from a mixed splenocyte population stimulated with antigen for a short period (6 days) in vitro. As such, these cells likely would not be suitable for identifying and generating both TCR α and β genes from a given T cell due to the heterogeneity of T cells present. Moreover, Chung et al. only discloses generating TCR α and β genes from an isolated human T-cell clone rather than the mixed splenocyte culture of Sette et al. Thus, the combined teachings of Sette et al. and Chung et al. would not lead one skilled in the art to produce a nucleic acid molecule encoding a non-human α/β TCR that is human HLA-restricted and specific for a tumor associated antigen.

Disis et al. teach identification of HER-2/neu tumor associated antigens by in vitro immunization in a culture system using human peripheral blood lymphocytes. This method is quite different from immunizing HLA-A2 mice and analyzing peptide-specific mouse CTLs. Sette shows that viral antigens recognized by human CTLs can differ from those immunogenic in HLA-A2/K^b mice. Based on the results presented in the current application, this also appears to be the case for the HER-2/neu antigens disclosed in Disis et al. For example, while Disis et al. describes two HER-2/Neu peptides capable of stimulating HLA-A2.1-restircted human CTL responses (Her-2/neu p48-56 and Her-2/neu p789-797 shown in Figure 1 of Disis), Applicants

found that these same peptides do not elicit T cell responses in immunized HLA-A2.1 transgenic animals (See Table 1 of the present application). Again, these findings indicate that, as discussed for Sette, results in other human T cell systems do not necessarily correspond to results in the non-human system of the present invention. So the methods of Disis are not instructive for selecting HER-2/neu antigens immunogenic in the non-human transgenic animal. In addition, Disis is silent on other tumor antigens (i.e. ras, p53, tyranase, MART, Gp100, Mage, BAGE or MUC-1) listed in claim 22 of the current application.

Accordingly, based on the foregoing, the claims are not obvious in view of the cited art. Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

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